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PCT/KR2004/002702

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference 04op122p	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. **PCT/KR2004/002702**	International filing date *(day/month/year)* **22 OCTOBER 2004 (22.10.2004)**	Priority date *(day/month/year)* 23 OCTOBER 2003 (23.10.2003)

International Patent Classification (IPC) or national classification and IPC

C07C 335/42(2006.01)i

Applicant

AMOREPACIFIC CORPORATION et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☒ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
02 MAY 2005 (02.05.2005)	12 JANUARY 2006 (12.01.2006)

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Box No. I Basis of the report

1. With regard to the **language,** this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this reort as "originally filed" and are not annexed to this report):*

   ☒ the international application as originally filed/furnished

   ☐ the description:
   pages _____ as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the claims:
   pages _____ as originally filed/furnished
   pages* _____ as amended (together with any statment) under Article 19
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the drawings:
   pages _____ as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)* : _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)*: _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 31,32

because:

☒ the said international application, or the said claims Nos. 31,32 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

The subject-matter of claims 31 and 32 do not require an international preliminary examination with respect to industrial applicability as it is a method of treating a mammal including man suffering from the pathological stimulation of VR1 recepters such as pain, migraine or urinary bladder hypersensitiveness, etc.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 31,32

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the techmical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-30, 33-35	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-30, 33-35	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-30, 33-35	YES
	Claims	None	NO

2. Citations and explanations (Rule 70.7)

References is made to the following documents:

D1: WO 02/16318 A1 (28 Feb. 2002)
D2: Bioorg. Med. Chem. Lett. 5(13), 1331-1334 (1995)
D3: US 6057451 (2 May 2000)

1. Novelty and Inventive Step

The present invention relates to inclusion compounds comprising thiourea derivatives of formula (I) or pharmaceutically acceptable salt thereof and a cyclodextrin or its derivatives as a solubility and bioavailability-improving carrier, and pharmaceutical formulation comprising the same.

D1 to D3 are considered to represent the most relevant state of the art. D1 discloses thiourea derivatives itself, D2 discloses thiourea derivatives having alkyl(octyl) chain at N-1 and methoxy group substituted benzyl group at N-3. D3 discloses urea derivatives.

Although, D1 discloses the same thiourea derivatives as the host molecule of the present invention, the type of compounds of D1 is quite different from that of compounds of the present invention in that the compounds of the present invention are *inclusion compounds* comprising thiourea derivatives as a host molecule and cyclodextrin as a guest molecule, whereas the compounds of D1 are *thiourea derivatives itself*.
The structures of the compounds of D2 and D3 also greatly differ from those of the compounds of the present invention in that the compounds of the present invention are the thiourea derivatives having methanesulfonylamino group or halogen substituted benzyl group at N-1 and N-3, whereas the compounds of D2 and D3 are thiourea derivatives having alkyl(octyl) chain at N-1 and methoxy group substituted benzyl group at N-3(D2) or urea derivatives(D3).

Furthermore, the inclusion compounds of the present invention show a significant difference in the time-dependent plasma concentration as compared with the compounds of D1, and their bioavailability is also about 4-folds higher than the compounds of D1 due to their improved solubility and dissolution rate.

Thus, the subject matter of the present claims 1-30 and 33-35 is considered to be novel and to involve an inventive step under PCT Article 33(2) and 33(3).

2. Industrial Applicability

There is no reason for denying industrial applicability of this invention. Consequently, claims 1-30 and 33-35 appear to meet the requirement of PCT Article 33(4).

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 5 to 8, 10 to 12, 14 to 20, 25 to 29, 31, 33 and 34 do not comply with Rule 6.4(a) because multiple dependent claims should not serve as a basis for any other multiple dependent clams.